PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference CPW/22452	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2004/000064	International filing date *(day/month/year)* 12.01.2004	Priority date *(day/month/year)* 15.01.2003
International Patent Classification (IPC) or national classification and IPC C07D401/12		
Applicant CIPLA LIMITED		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 5 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.08.2004	19.05.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Fazzi, R Telephone No. +49 89 2399-8510

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/000064

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-14 as originally filed

   Claims, Numbers

   1-34 received on 12.11.2004 with letter of 12.11.2004

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☒ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☒ the claims, Nos. 35-40
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 1-8, 10-13
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 31-34

because:

☒ the said international application, or the said claims Nos. 31-34 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	9
	No:	Claims	14-34
Inventive step (IS)	Yes:	Claims	
	No:	Claims	9, 14-34
Industrial applicability (IA)	Yes:	Claims	9, 14-30
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1) Reference is made to the following documents:

D1: US-A-6 017 560
D2: US-A-5 708 013
D3: EP-A-0 533 264
D4: EP-A-0 134 400
D5: GB-A-2 134 523
D6: VYAS K ET AL: 'LANSOPRAZOLE, AN ANTIULCERATIVE DRUG' ACTA CRYSTALOGRAPHICA SECTION C. CRYSTAL STRUCTURE COMMUNICATIONS, MUNKSGAARD, COPENHAGEN, DK, vol. C56, no. 12, 2000, pages E572-E573, XP009014904 ISSN: 0108-2701
D7: GRAUL A ET AL: 'ESOMEPRAZOLE MAGNESIUM (-)-OMEPRAZOLE MAGNESIUM PERPRAZOLE (FORMERLY) (S)-OMEPRAZOLE MAGNESIUM H-199/18 NEXIUM' DRUGS OF THE FUTURE, BARCELONA, ES, vol. 24, no. 11, 1999, pages 1178-1183, XP009026689 ISSN: 0377-8282
D8: WILLIAMS M P ET AL: 'Review article: the pharmacology of rabeprazole' ALIMENTARY PHARMACOLOGY & THERAPEUTICS, BLACKWELL SCIENTIFIC PUBLICATIONS LTD., CAMBRIDGE, GB, vol. 13, no. 3, 1999, pages 3-10, XP002963613 ISSN: 0269-2813
D9: GARNER A ET AL: 'PANTOPRAZOLE: A NEW AND MORE SPECIFIC PROTON PUMP INHIBITOR' EXPERT OPINION ON INVESTIGATIONAL DRUGS, ASHLEY PUBLICATIONS LTD., LONDON, GB, vol. 6, no. 7, 1997, pages 885-893, XP009025982 ISSN: 1354-3784

1.1) Reference to section I

The amendments filed with letter dated 12/11/2004 introduce subject-matter which extends beyond the content of the application as originally filed, so as **not** to comply with the requirements of Articles 19(2) and 34(2b) PCT.
As the Applicant did not explain on which part of the application the cited amendments were based, the following reasonings should be taken into consideration:

(a) if the Applicant based present claims on old independent claim 1, then the amendments concern the deletion of the feature *characterized in that the pH of the reaction mixture at least*

during said oxidation is in the range of 9 to 12, which was present in original claim 1, and which is considered **essential** for the definition of the subject-matter of the current application.

(b) if the Applicant based present claims on old independent claim 3, then the amendments concern the introduction of the feature of *an alkali or alkali earth metal hydroxide*, which is *added to a suspension of formula II*, before the oxidising agent is introduced.
This feature has a basis in previous claim 15, but, again, the feature *whereby a pH in the range of 9 to 12 is obtained for said reaction mixture at least during said oxidation,* is missing.

Accordingly, the present International Preliminary Report is based on present claim 9, which appears to be based on previous claim 1 in combination with previous claims 2, 9 and 13.
The substitution of the wording *alkali* with *alkali or alkali earth metal hydroxide* has been accepted (cf. annex from the Encyclopaedia Britannica).

2) Reference to section III

Claims 31-34 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

3) Novelty (Reference to section V)

D1 discloses on column 4 (lines 1-16) a process for converting a compound of formula (II) to a compound of formula (I) in the presence of an oxidizing agent, which may be sodium hypochlorite. The presence of an alkali or alkali earth metal hydroxide is not mentioned.

D2, D4 and D5 do not overlap with the subject-matter of present claim 9 as they do not disclose the addition of an oxidising agent comprising an aqueous alkali or alkali earth metal hypohalite solution to an existing solution containing a compound of present formula II and an alkali or alkali earth metal hydroxide.

The teaching of D3 does not involve the presence of an oxidising agent comprising an aqueous alkali or alkali earth metal hypohalite solution.

The subject-matter of present claim 9 thus meets the criteria of Article 33(2) PCT.

As concerns the subject-matter of present claims 14-34, it should be noticed that compounds of formula (I) are well-known drugs (lansoprazole, omeprazole, pantoprazole and rabeprazole, which can be also demonstrated by D6-D9), which are not rendered new by the fact that they are prepared by a different process.

Thus, the subject-matter of claims 14-34 does not meet the requirements of Article 33(2) PCT.

4) Inventive step (Reference to section V)

The Examiner agrees with the Applicant that D4 may be considered to represent the closest state of the art. This document discloses in fact on page 13 that compounds of formula (VIII) may be oxidized in the presence of an aqueous hypohalite solution (cf. also end of page 15 and beginning of page 16).
The problem to be solved by the present application may therefore be regarded as the provision of a further process for the preparation of compounds of formula (I).
Example 2 of D4 further discloses the presence of sodium hydroxide, which is added at the same time with a sodium hypochlorite solution to the reaction mixture.
In present claim 1, however, the alkali or alkali earth metal hydroxide is added before the alkali or alkali earth metal hypohalite solution having a concentration in the range of 2 to 5%.
However, such a difference is deemed to be obvious in view of the teaching of D4, as the addition of said base before, after or at the same time with the hypohalite solution could be arrived at by routine trial and error or by application of normal design procedure.
In the absence of any evidence in the application, that the process of present claim 9 involves unexpected effects or properties over the prior art, the subject-matter of said claim is considered not to meet the requirements of Article 33(3) PCT.

5) Industrial applicability (Reference to section V)

For the assessment of the present claims 31-34 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical

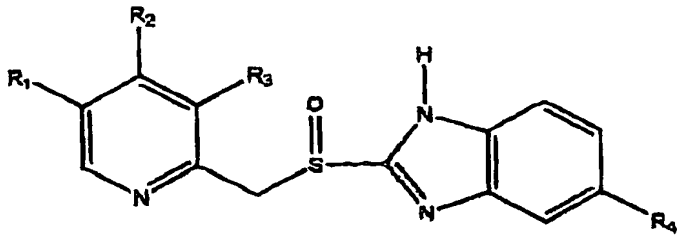
treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

6) Further observations (Reference to section VIII)

The relative term "substantially free" used in the whole application has no well-recognised meaning and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of the claims unclear (Article 6 PCT).

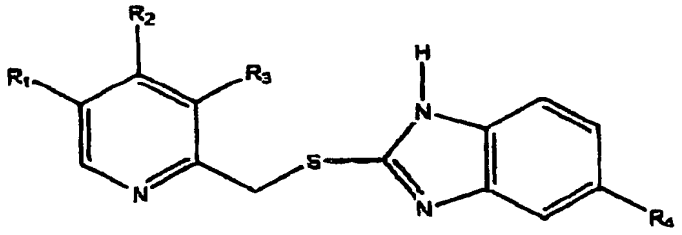
CLAIMS

1. A process for preparing a sulfinyl compound of formula (I), or a pharmaceutically acceptable salt, hydrate or solvate thereof,



(I)

which process comprises oxidation of a sulfide compound of formula (II)



(II)

wherein in both formulae (I) and (II) R_1 and R_3 are selected from the group consisting of hydrogen, methyl or C_{1-4}alkoxy, R_2 is selected from the group consisting of substituted or unsubstituted C_{1-4}alkoxy and R_4 is selected from the group consisting of hydrogen or substituted or unsubstituted C_{1-4}alkoxy;

characterised in that a solution of an alkali or alkali earth metal hydroxide is added to a suspension or solution of a sulfide compound of formula (II), and thereafter there is added thereto an oxidising agent comprising an aqueous alkali or alkali earth metal hypohalite solution, having a concentration in the range of 2 to 5%, such that a sulfide compound of formula (II) is oxidised to a sulfinyl compound of formula (I) in the presence of the alkali or alkali earth metal hydroxide, and optionally converting a

sulfinyl compound of formula (I) to a pharmaceutically acceptable salt, hydrate or solvate thereof.

2. A process according to claim 1, wherein a compound of formula (II) is reacted with an aqueous hypohalite solution in the presence of a catalyst selected from the group consisting of pyridine, di-isopropyl ethyl amine and N,N-dimethyl amino pyridine.

3. A process according to claim 1 or 2, which comprises dissolving or suspending a compound of formula (II) in a solvent selected from the group consisting of water, lower alkyl alcohols, esters, ethers and chlorinated solvents, or a mixture of two or more of these solvents.

4. A process according to claim 3, wherein said solvent is selected from the group consisting of water, methanol, ethanol, isopropanol, di-isopropyl ether, dichloromethane, acetonitrile and ethyl acetate, or a mixture of two or more of these solvents.

5. A process according to any of claims 1 to 4, which is carried out at a temperature in the range of –30 to 50°C.

6. A process according to claim 5, which is carried out at a temperature in the range of 0 to 30°C.

7. A process according to any of claims 1 to 6, wherein said alkali metal or alkali earth metal hypohalite is selected from the group consisting of sodium hypochlorite, sodium hypobromite and calcium hypochlorite.

8. A process according to claim 7, wherein said aqueous hypohalite solution comprises sodium hypochlorite.

9. A process according to any of claims 1 to 8, wherein a pH in the range of 9 to 12 is obtained at least during said oxidation.

10. A process according to any of claims 1 to 9, wherein in formula (I) R_1 represents methyl, R_2 represents trifluoroethoxy, R_3 represents hydrogen and R_4 represents hydrogen.

11. A process according to any of claims 1 to 9, wherein in formula (I) R_1 represents methyl, R_2 represents methoxy, R_3 represents methyl and R_4 represents methoxy.

12. A process according to any of claims 1 to 9, wherein in formula (I) R_1 represents methoxy, R_2 represents methoxy, R_3 represents hydrogen and R_4 represents difluoromethoxy.

13. A process according to any of claims 1 to 9, wherein in formula (I) R_1 represents methyl, R_2 represents $OCH_2CH_2CH_2OMe$, R_3 represents hydrogen and R_4 represents hydrogen.

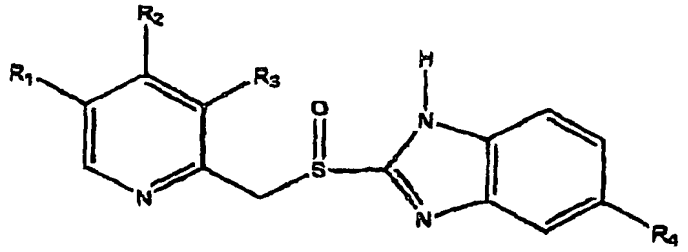
14. Lansoprazole prepared according to claim 10, substantially free of oxidation contamination by products.

15. Omeprazole prepared according to claim 11, substantially free of oxidation contamination by products.

16. Pantoprazole prepared according to claim 12, substantially free of oxidation contamination by products.

17. Rabeprazole prepared according to claim 13, substantially free of oxidation contamination by products.

18. A pharmaceutical composition comprising a sulfinyl compound of formula (I)



(I)

wherein R_1 and R_3 are selected from the group consisting of hydrogen, methyl or C_{1-4}alkoxy, R_2 is selected from the group consisting of substituted or unsubstituted C_{1-4}alkoxy and R_4 is selected from the group consisting of hydrogen or substituted or unsubstituted C_{1-4}alkoxy;

prepared according to any of claims 1 to 13, together with a pharmaceutically acceptable carrier or excipient therefor.

19. A pharmaceutical composition comprising lansoprazole according to claim 14, together with a pharmaceutically acceptable carrier or excipient therefor.

20. A pharmaceutical composition comprising omeprazole according to claim 15, together with a pharmaceutically acceptable carrier or excipient therefor.

21. A pharmaceutical composition comprising pantoprazole according to claim 16, together with a pharmaceutically acceptable carrier or excipient therefor.

22. A pharmaceutical composition comprising rabeprazole according to claim 17, together with a pharmaceutically acceptable carrier or excipient therefor.

23. For use in therapy, lansoprazole according to claim 14.

24. For use in therapy, omeprazole according to claim 15.

25. For use in therapy, pantoprazole according to claim 16.

26. For use in therapy, rabeprazole according to claim 17.

27. For use in the manufacture of a medicament for the treatment of gastric ulcers and related conditions, lansoprazole according to claim 14.

28. For use in the manufacture of a medicament for the treatment of gastric ulcers and related conditions, omeprazole according to claim 15.

29. For use in the manufacture of a medicament for the treatment of gastric ulcers and related conditions, pantoprazole according to claim 16.

30. For use in the manufacture of a medicament for the treatment of gastric ulcers and related conditions, rabeprazole according to claim 17.

31. A method of treating gastric ulcers and related conditions, which comprises administering to a patient in need of such treatment lansoprazole according to claim 14.

32. A method of treating gastric ulcers and related conditions, which comprises administering to a patient in need of such treatment omeprazole according to claim 15.

33. A method of treating gastric ulcers and related conditions, which comprises administering to a patient in need of such treatment pantoprazole according to claim 16.

34. A method of treating gastric ulcers and related conditions, which comprises administering to a patient in need of such treatment rabeprazole according to claim 17.